Update by Professor Jürgen Hescheler on the status of stem cell research

“We are not taking the leap”

When can we expect to grow new teeth in order to replace lost teeth? Back in 2014, the EDI Journal editors have spoken with famous German stem cell researcher Professor Jürgen Hescheler from Cologne. Now, three years later and with the International Dental Show coming up in March, we asked for an update and were rather surprised. Hescheler is part of a team consisting of a hundred internationally recognized experts who regularly meet at the University of Beijing to discuss the viability of different types of stem cells. Germany is not doing very well in the field of stem cell research. There is a lack of moral and financial support. Editor-in-Chief Anita Wuttke spoke with Professor Hescheler.

What are you working on right now?

Our institute carries out research on the subject of pluripotent stem cells, that is, cells that are “all-rounders” and can develop into any kind of tissue. In particular, we are working to develop cardiac muscle cells to treat myocardial infarction.

The Institute of Neurophysiology also has a working group that looks into the development of neural cells and their integration into the brain. However, this group is smaller than the cardiac muscle group because we expect faster therapeutic success in this area; after all, the heart is much less complicated than the brain. I would also like to mention our working group for the development of blood cells, which has been off to a good start with a successful cooperation and decent funding.

Nevertheless, I am also still very interested in the development of teeth and bone. I have presented the subject on many occasions. Not to forget 3D printing – creating tissue by biological engineering.

Is that something new in your field?

It actually is. In the past few years, we have learned a lot about the development of stem cells in tissues, that is in connection with other cells (for example connective tissue cells) and in matrices with different mechanical and physical properties. These findings have a fundamental importance for bioengineering. We already use 3D printers for printing the substrates on which we grow stem cells.

In future, however, we would also very much like to investigate bio-printing with “bio-ink”, where the aim is to print cells, which can then be built up, layer by layer, to form tissue.

What progress has been made in stem cell research in the three years since our last interview?

There have been a number of developments, but nothing revolutionary. For example, what has improved significantly in recent years are the directed differentiation protocols, which means that we now know quite well what growth and differentiation factors must be added to a culture so that the pluripotent stem cells develop in a specific direction. Previously, we mostly dealt with spontaneous differentiation; now we can influence the process very selectively using those factors.

Professor Jürgen Hescheler

Professor Hescheler, Director of the Institute of Neurophysiology at the University Hospital Cologne, has been working with embryonic stem cells for over 20 years. Beginning with studies on cellular signal transduction, he has defined many important fundamental aspects both for basic research and for clinical applications. He has a strong interest in the therapeutic application of ES and iPS cells.

What results were achieved in world-wide stem cell research in the past three years?

There has been no great breakthrough I could tell you about. One of the up-and-coming topics is the so-called organoid. This is actually an old idea: Stem cells are grown in 3D cultures where they develop into organ-like structures, instead of the flat cellular layers that have been common until now. Actually, we have already been applying this idea at the beginning of our research in the "embryoid body" cultures as a model of early embryonic development.

The interesting thing about the organoids, which are for example developed as "mini-brains" or liver organoids, is the finding that for every organ, not one single type of cell is important, but that different types of cells cooperate in the organ to develop their organotypical function.

More complex organ structures arise from the cooperation of two or more cell types – and this is how teeth develop from stem cells. This insight is important because it helps us build new test systems for pharmacology and toxicology from stem cells.

But for now there are no results that can be turned into products?

Unfortunately, no! In my opinion, stem cell research is currently in a crisis. Actually, it has already grown beyond being basic research, and we are focusing on its applications. But the applications have not yet reached the point where you can make money with them. We have a funding gap. For private companies it is still too early to invest money, while for the sponsors of basic research – such as the German Federal Ministry of Education and Research or the German Research Foundation – we are already too far into applied science. And until now, stem cell research has not yet managed to overcome this hurdle.

We need more investment in stem cell research and its therapeutic application. The research methods required now go far beyond what an institute such as the one I lead at the university can achieve. The next crucial step would have to be conclusive experiments on large mammals to prepare the clinical studies. But this is almost impossible to do in Germany, because it causes huge costs, which a university research institute like ours simply cannot afford. GMP (good manufacturing practice) production would also be necessary now, that is, the cells would need to be produced under highly sterile conditions so that they can subsequently be used in future therapy. We fall short on all these areas ...

... only in Germany or all over the world?

Definitely in Germany. Globally, things look better. The Japanese are already way ahead of us. They have built a new, very well equipped institute that has everything I have been talking about, for *Professor Shinya Yamanaka*. He is the 2012 Nobel Prize winner in medicine, and receives very high financial support. I was fortunate in that he invited me to his lecture in Kyoto recently so that I could see how impressing and successful their research is. The breakthrough in the application of stem cell research is likely to happen in Asia.

The USA, too, spend relatively large sums in this field. And as far as your question about innovations goes, I would also like to mention the work of *Robert Lanza*, who transplanted eye cells derived from pluripotent stem cells in patients with macular degeneration and thereby improved their vision significantly. Since then, already three years have passed, but it has been the last breakthrough we have had in the field of stem cell research on its way to clinic. Clinical studies on paraplegia and muscular dystrophy have been registered internationally.

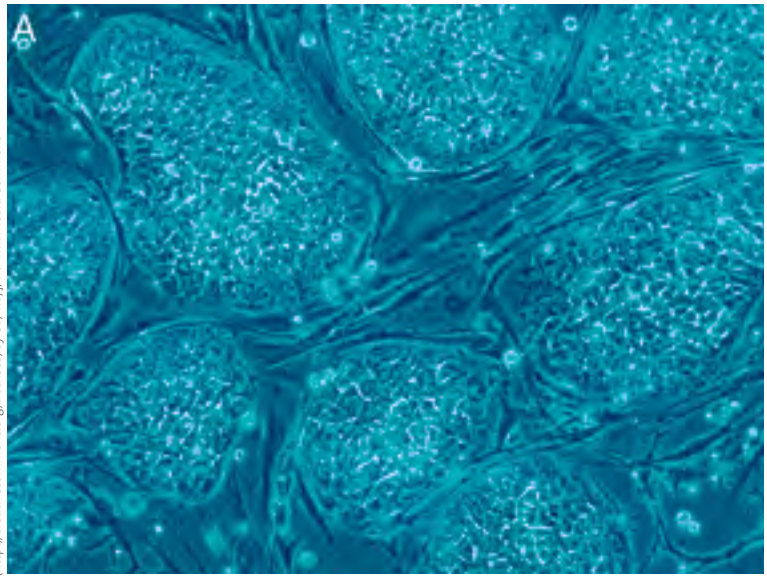
How about the political support for stem cell research in Germany?

I am afraid it is a total disaster. My people spend nearly 90 per cent of their time writing complicated and extensive applications. Their scientific work falls by the wayside.

In Germany, it is extremely difficult to raise funds for stem cell research. The major funding programmes for our field of research have been scaled down continuously. Only five years ago, there were more extensive national and European funding programmes, especially in regenerative medicine, but those were unfortunately discontinued. The projects they supported may have promised too much too soon in terms of therapeutic applications of adult stem cells. So we were stopped halfway down the road.

What is the current status in Germany and in Europe in the field of stem cell research?

We have fallen behind and nearly become third-rate. European funding has also decreased. My work often takes me to Asia, and when you see how well the institutes are equipped and financially supported there, I would already put Japan, Singapore and China in the front row. The USA and Canada do not look that bad, either.



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Human embryonic stem cells.

What about India?

I used to have more contacts with India. Unfortunately, research there is not structured in the same way as in China. China spends billions on innovative techniques and systematically built research and development parks during the past years, where the universities' research results are actively implemented and innovative new companies are founded and supported.

This publication is of course interested in the topic of "renewable teeth". Has anything serious happened here since 2014? What is the current state of affairs?

Current publications worldwide have shown clearly that human induced pluripotent stem cells have been used to produce human teeth. Practical application is still limited to small animals. There have been no tests on large mammals worldwide, at least none have been published. But this would be an important prerequisite for clinical therapy in humans. Again – as with all areas of stem cell research – we have now reached the border between basic research and application.

As I said, the problems we encounter in that area are much greater than we expected some years ago. But they are of a purely economic rather than scientific nature.

I am repeating my question of three years ago: When will we be starting to see the first renewable tooth on the market? Three years ago you were talking about ten or 20 years …?

I stand by what I already said back then: We could succeed in ten years' time – if we received the necessary funds. For example, together with Professor Zöller, who is the director of the Interdisciplinary Department of Oral Surgery and Implantology at the University of Cologne, we made attempts to acquire funding for the development of teeth and bone for implantology in Germany, and to advance its development. Unfortunately, we were rejected again and again. We had some interested investors, but they unfortunately withdrew because the business case is still rather unclear at this point.

What does the development of a renewable tooth cost?

This is a quite a difficult question. The prototypes would of course be very expensive, because one would have to include the development cost. But

once we have a routine and calculate only the cost of materials and labour – roughly between 100 and 500 euros. Add to this the high licence fees (certainly more than 10,000 euros) for any patent applications filed abroad.

And there is another question that has cost implications: Will the tissue be grown in a bioreactor and implanted as a finished tooth, or can we implant a tooth germ that would then grow in vivo?

Do you still believe that the renewable tooth can become a reality?

Yes, I am convinced of that. Just as I am convinced of success and breakthrough in all other areas of stem cell research and regenerative medicine. If there is a breakthrough somewhere and investors flock in, then things can happen very quickly.

Ultimately, we are all convinced that this will be a revolution in medicine and dentistry. The application of stem cells and therapeutic cell agents derived from them could help to cure many diseases that have not been curable and where drugs are of no help. One of these days we will certainly get there.

To return to your tooth: Biotech companies could well produce precisely fitting prefabricated tooth germs or fully grown teeth that can then be implanted in case of tooth defects – new teeth made to order, so to speak.

So oral implantologists will not be unemployed?

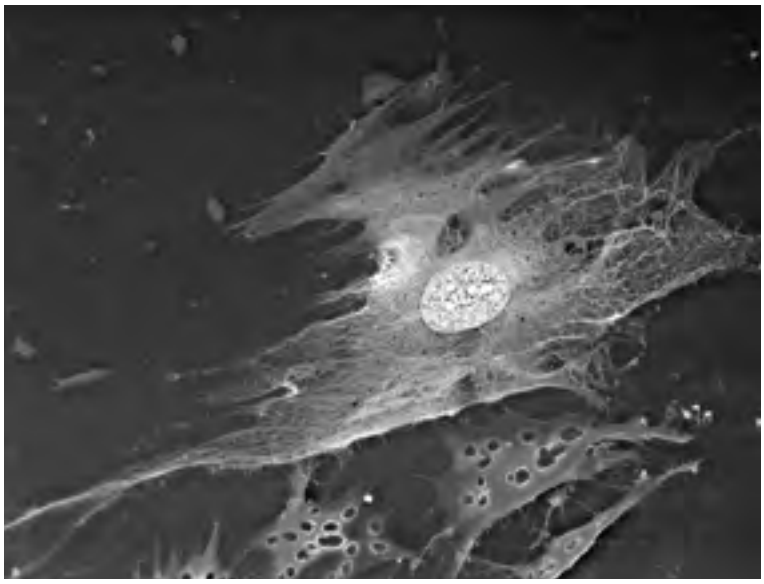
Their field will change. What they will implant is not inert fixtures but tooth germs or fully grown teeth.

But patient welfare should always be in focus and rank first. It is always better to have a natural tooth. And that would certainly be a step forward for the patient. Oral implantologists will have to focus more closely on the biological status of the jaw and cooperate more closely with biotech firms. But working on and with patients will remain the domain of oral implantologists.

What global innovations can we expect from stem cell research?

For me, the translational aspect is important, that is to take stem cell research from basic research to clinic. The scientific innovations in stem cell research have been accomplished in the past, but we have already seen a lot of innovation. Everything now comes down to the technical innovation and their application in clinical practice.

Our research institute, for example, is heavily involved in the regeneration aspect to apply stem cells in curing myocardial infarction. Beyond aspects of regenerative medicine, a major potential for innovation that I see in stem cell research is the development of innovative human testing systems for the industry. We engaged, for example, in a major European project together with the cosmetics industry to identify and evaluate harmful substances in cosmetics. A promising approach, because it is easier to test this with human cells.



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Dental pulp stem cells on tissue culture plastic.

We have also invested a lot in exploring stem cell genomes, that is, the genetic modifications in developing cells. We will gain a deeper understanding of the mechanisms of stem cells to learn why and how the specialized – organotypical – cells of organs develop from pluripotent stem cells.

Finally, the "ten thousand euro question". What do you expect from politicians in Germany?

Greater interest of course, but also more support and better funding. And we would like to see more done that could bring together the groups that carry out research in related fields.

That was your wish three years ago ...

... true, and unfortunately it still is today.

Thank you very much for this interesting interview, Professor Hescheler. ■

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